What effect does folic acid supplementation (with or without additional B vitamin supplementation) have on risk of CVD among persons with or without pre-existing vascular disease?

Conclusion

Strong evidence demonstrates that folic acid supplementation with or without additional B vitamins in adult men and women with pre-existing vascular disease, does not appear to reduce risk of cardiovascular disease, and may increase risk slightly.

Grade: Strong

Overall strength of the available supporting evidence: Strong; Moderate; Limited; Expert Opinion Only; Grade not assignable For additional information regarding how to interpret grades,click here.

Evidence Summary Overview

Four large randomized placebo controlled trials (CT) and one meta-analysis study examined the relationship between folic acid supplementation and risk of cardiovascular disease (CVD) in adults with pre-existing vascular disease.

Albert et al (2008) (positive quality) conducted an CT as part of an ongoing antioxidant vitamin trail with health professionals in the US. Women aged 40 and older were randomized to either placebo or a supplement containing folic acid (2.5mg), vitamin B_{12} (mg) and vitamin B_6 (50mg). All women had a history of CVD or three or more coronary risk factors (average age. 62.8 years). The average follow-up was 7.3 years. The primary outcome was composite of myocardial infarction, stroke, coronary revascularization or CVD mortality. Again, despite significant homocysteine lowering, the folic acid, B_{12} and B_6 vitamin supplement did not reduce cardiovascular events (RR 1.03; 95% CI: 0.90 to 1.19; P=0.65). The authors noted that a limitation of the study was that the research subjects were health professionals and at low risk for folate deficiency. In addition, all subjects were exposed to universal folate fortification of grain at the time the study. Therefore, one cannot rule out the benefit of folate supplementation in a folate-deficient population.

Ebbing et al (2008) (positive quality) conducted an CT in Norway as part of the Western Norway B-Vitamin Intervention Trial. Men and women aged 18 or older from two hospitals in western Norway who where undergoing coronary artery angiography for suspectedCVD or aortic valve stenosis were included in the trial. A total of 3,096 patients were randomized (mean age 61.7 years, 20.5% female). A total of 2,121 patients completed the trial. The researchers used a 2 x 2 factorial design. Patients were randomized to a placebo or one of three different daily supplements: 1) Folic acid (0.8mg), plus vitamin B_{12} (0.4mg) and B_6 (40mg); 2) Folic acid (0.8mg), plus B_{12} (0.4mg); vitamin B_6 (40mg). The median follow-up was 38 months. The primary outcome was a composite of all-cause death, non-fatal acute myocardial infarction (MI), acute hospitalization or unstable

angina pectoris, and non-fatal thromboembolic stroke. Mean plasma homocysteine concentration decreased by 30% after one year of treatment. Despite these reductions, overall there was no effect of the treatment with folic acid and vitamin B_{12} or vitamin B_6 on total mortality or cardiovascular events. If anything there was a slight but significant increase in risk using post-hoc overall survival analysis of the composite primary endpoint in the group receiving folic acid plus vitamin B_{12} (HR, 1.43; 95% CI: 1.03 to 1.75; P=03) compared to placebo.

Ray et al (2007) (positive quality) conducted a placebo-controlled clinical trial using data from the Heart Outcomes Prevention Evaluation 2 (HOPE-2), a large (N=5,522), five-year randomized study, to determine whether decreasinghomocysteine levels alters the risk for symptomatic venous thromboembolism. The vitamin therapy group received a daily supplement containing 2.5mg of folic acid, 50mg of vitamin B_6, and mg of vitamin B_{12}. The incidence rate of venous thromboembolism was the same in the vitamin therapy group and the placebo group (0.35 per 100 person-years; hazard ratio (HR), 1.01; 95% CI: 0.66, 1.53). Vitamin therapy did not reduce the risk for deep venous thrombosis (HR, 1.04; 95% CI: 0.63, 1.72), pulmonary embolism (HR, 1.14; 95% CI: 0.57, 2.28), or unprovoked venous thromboembolism (HR, 1.21; 95% CI: 0.66, 2.23). Decreasing homocysteine levels with folic acid and vitamins B_6 and B_{12} did not reduce the risk for symptomatic venous thromboembolism.

Bonaa et al (2006) (positive quality) conducted a randomized controlled trial (RCT), double-blind, 2 x 2 factorial design evaluated data from men and women 30 to 85 years of age who had had an acute MI from the Norwegian Vitamin (NORVIT) trial. Vitamin B treatments had no significant (NS) effect on the primary end point (risk ratio, 1.08; 95% CI: 0.93, 1.25; P=0.31). Treatment with vitamin B_6 was not associated with any significant benefit with regard to the primary end point [relative risk (RR) of the primary end point, 1.14; 95% CI: 0.98, 1.32; P=0.09]. In the group given folic acid, vitamin B_{12} and vitamin B_6, there was a trend toward an increased risk (RR, 1.22; 95% CI: 1.00, 1.50; P=0.05). Treatment with B-vitamins did not lower the risk of recurrent cardiovascular disease after acute MI. In this trial, a harmful effect from combined B-vitamin treatment was suggested.

Bazzano et al (2006) (positive quality) was a meta-analysis. The objective of the metal-analysis was to evaluate the effects of folic acid supplementation on risk of CVD and all-cause mortality among adults with pre-existing CVD or renal disease. The researchers only evaluated RCTs. Studies were retrieved by searching Medline from January 1966 to July 2006. Out of a total of 165 studies reviewed, 12 studies met the criteria for inclusion, representing 16,958 men and women. The studies were conducted around the world (two in the US, one in Australia and New Zealand, one in Canada and eight in Europe). Dosage of folic acid supplementation ranged from 0.5mg per day to 15mg per day and study durations ranged from six months to five years. In this metal-analysis, folic acid supplementation did not reduce risk of CVD or all-cause mortality in persons with prior history of disease. The overall RR of outcomes for subjects receiving folic acid supplementation compared to controls were 0.95 (95% CI: 0.88 to 1.03) for CVD, 1.04 (95% CI: 0.92 to 1.17) for coronary heart disease (CHD) and 0.96 (95% CI: 0.88 to 1.04) for all-cause mortality.

These data taken together demonstrate consistent outcomes showing that folic acid supplementation does not reduce risk of CVD in men and women with existing disease. There is some limited evidence that there may be increased risk. For this reason, adults with pre-existing vascular disease should not be encouraged to take a folic acid supplementation. One question that still remains is whether there are any differences in response due to race or ethnicity with folic acid supplementation.

Evidence Summary Paragraphs

Albert et al, 2008 (positive quality). This RCT (individually randomized) tested whether a combination of 2.5mg of folic acid, 50mg of vitamin B_6 and mg of vitamin B_{12} lowers risk of CVD among high-risk women with and without CVD. The study participants were from the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), aged 40 years or older, post-menopausal or with no intention of becoming pregnant, and had a reported history of CVD or had at least three cardiac risk factors. The results showed that 796 participants (14.6%) from a total of 5,442, experienced a confirmed CVD event (139 MIs, 148 strokes, 508 coronary revascularization procedures and 190 cardiovascular deaths). There was no difference in the cumulative incidence of the primary combined endpoint in the active vs. placebo treatment groups at any time during study follow-up. In addition, 406 women (14.9%) in the active treatment group and 390 (14.3%) in the placebo group experienced at least one cardiovascular event included in the primary endpoint (226.9 per 10,000 person-years vs. 219.2 per 10,000 person-years). The overall RR was 1.03 (95% CI: 0.90,1.19; P=0.65) after controlling for age and antioxidant treatment assignment. In conclusion, after 7.3 years of treatment and follow-up, a combination pill of folic acid, vitamin B_6 and vitamin B_{12} did not reduce a combined endpoint of total cardiovascular events among high-risk women.

Bazzano et al, 2006 (positive quality). This meta-analysis study evaluated the effects of folic acid supplementation on risk of CVD and all-cause mortality using a random-effects model. The 12 RCTs represented 16,958 men and women. The overall RR CIs of outcomes for patients treated with folic acid supplementation compared with controls were 0.95 (0.88,1.03) for CVD, 1.04 (0.92,1.17) for CHD, 0.86 (0.71,1.04) for stroke and 0.96 (0.88,1.04) for all-cause mortality. The RR was consistent among participants with pre-existing CVD or renal disease. Folic acid supplementation has not been shown to reduce risk of CVD or all-cause mortality among participants with prior history of vascular disease. Studies included US, Canadian and European subjects.

Bonaa et al, 2006 (positive quality). This RCT, double-blind, 2 x 2 factorial design evaluated data from men and women 30 to 85 years of age who had had an acute MI from the Norwegian Vitamin (NORVIT) trial. Vitamin-B treatments had NS effect on the primary end point (RR, 1.08; 95% CI: 0.93, 1.25; P=0.31). Also, treatment with vitamin B_6 was not associated with any significant benefit with regard to the primary end point (RR of the primary end point, 1.14; 95% CI: 0.98, 1.32; P=0.09). In the group gimetalfolic acid, vitamin B_{12} and vitamin B_6, there was a trend toward an increased risk (RR, 1.22; 95% CI: 1.00, 1.50; P=0.05). Treatment with B vitamins did not lower the risk of recurrent CVD after acute MI. In this trial a harmful effect from combined B-vitamin treatment was suggested.

Ebbing et al, 2009 (positive quality). This randomized double blind controlled trial assessed the effect of treatment with folic acid and vitamin B_{12} and the effect of treatment with vitamin B_6 as secondary prevention. Data from the Western Norway B-vitamin intervention Trial (WENBIT) was used; it included men and women 18 years old or older undergoing coronary artery angiography for suspected coronary artery disease (CAD) or aortic valve stenosis from two university hospitals in Western Norway. Intervention treatment consisted of daily oral dose of one of the following: 1) Folic acid, 0.8 mg, plus vitamin B_{12} (cyanocobalamin), 0.4mg and vitamin B_6 (pyridoxine), 40mg; 2) Folic acid, 0.8mg, plus vitamin B_{12}, 0.4mg; 3) Vitamin B_6, 40mg; or 4) Placebo. Mean follow-up was 38 months. Results after one year showed mean serum folate concentration increased seven-fold and mean serum cobalamin concentration increased by 65% in the groups receiving folic acid plus vitamin B_{12}. Mean plasma total homocysteine level was decreased by 30%, from 10.8 (SD, 4.5) μmol per L at baseline to 7.6 (SD, 2.2) μmol per L in the groups receiving folic acid and vitamin B_{12} ($P<0.001$). In the final results, 422 participants (13.7% of all) experienced an event in the composite primary end point of death, acute MI (AMI), unstable angina pectoris or thromboembolic stroke. A total of 219 participants (14.2%) in the groups receiving folic acid vs. 203

participants (13.1%) in the groups not receiving folic acid experienced the primary end point (HR=1.09; 95% CI: 0.90,1.32; P=0.36). 157 participants (12.2%) in the groups receiving folic acid groups vs. 146 (11.8%) of those not receiving folic acid experienced the primary end point (HR, 1.04; 95% CI: 0.83,1.30; P=0.75). There were no differences in treatment response for the separate end points of death, total AMI (fatal and non-fatal, including procedure-related), or unstable angina pectoris. The incidence of total stroke (fatal and non-fatal, including hemorrhagic) was NS lower in the groups receiving folic acid. The incidence of acute hospitalization due to angina pectoris was lower in the folic acid groups (HR= 0.82; 95% CI: 0.67,1.00; P=.05). Post-hoc overall survival analysis showed no differences between the groups (P=0.07), but there was an increased risk of the composite primary end point in the group receiving folic acid plus vitamin B_{12} (HR= 1.34; 95% CI: 1.03,1.75; P=0.03) compared with placebo. Daily supplements: 1) Folic acid (0.8mg), plus vitamin B_{12} (0.4mg) and B_6 (40mg); 2) Folic acid (0.8mg), plus B_{12} (0.4mg); vitamin B_6 (40mg). The median follow-up was 38 months. The primary outcome was a composite of all-cause death, non-fatal AMI, acute hospitalization or unstable angina pectoris and non-fatal thromboembolic stroke. Mean plasma homocysteine concentration decreased by 30% after one year of treatment. Despite these reductions, overall there was no effect of the treatment with folic acid and vitamin B_{12} or vitamin B_6 on total mortality or cardiovascular events. If anything, there was a slight but significant increase in risk using post-hoc overall survival analysis of the composite primary end point in the group receiving folic acid plus vitamin B_{12} (HR=1.43; 95% CI: 1.03,1.75; P=0.03) compared to placebo.

Ray et al, 2007 (positive quality). This placebo-controlled clinical trial used data from the Heart Outcomes Prevention Evaluation 2 (HOPE-2), a large, randomized study, to determine whether decreasing homocysteine levels alters the risk for symptomatic venous thromboembolism. The incidence rate of venous thromboembolism was the same in the vitamin therapy group and the placebo group (0.35 per 100 person-years; HR, 1.01 95% CI: 0.66, 1.53). Vitamin therapy did not reduce the risk for deep venous thrombosis (HR, 1.04; 95% CI: 0.63, 1.72), pulmonary embolism (HR, 1.14; 95% CI: 0.57, 2.28), or unprovoked venous thromboembolism (HR, 1.21; 95% CI: 0.66, 2.23). Decreasing homocysteine levels with folic acid and vitamins B_6 and B_{12} did not reduce the risk for symptomatic venous thromboembolism.

View table in new window

Author, Year, Study Design, Class, Rating	Population/Sample Description	Measurements or Intervention	Significant Outcomes
Albert CM, Cook NR et al, 2008 Study Design: Randomized controlled trial (individual randomized) Class: A	Participants from the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), age ≥42 years, post-menopausal or had no intention of becoming pregnant and had reported history of CVD or had at least three cardiac risk factors	Daily placebo or a combination pill containing 2.5mg folic acid, 50mg vitamin B_6 and 1mg vitamin B_{12}. Dietary folic acid intake.	N=796 participants (14.6%) from a total of 5,442 experienced a confirmed combined endpoint of cardiovascular morbidity and mortality event (139 MIs, 148 strokes, 508 coronary revascularization procedures and 190 cardiovascular deaths).

Class: A Rating:	cardiac risk factors.		No difference in cumulative incidence of primary combined end point in active vs. placebo treatment groups at any time during study follow-up. N=406 women (14.9%) in active treatment group and 390 (14.3%) in placebo group experienced at least one cardiovascular event included in the primary end point (226.9 of 10,000 person-years vs. 219.2 of 10,000 person-years). RR was 1.03 (95% CI: 0.90,1.19; P =0.65) after controlling for age and antioxidant treatment assignment. In separate analysis: NS differences between groups for each of the components of the primary outcome including CVD mortality (50.3/10,000 person-years vs. 49.6/10,000 person-years; RR= 1.01; 95% CI: 0.76,1.35; P = 0.93). No difference between groups for risk of death from any cause (RR= 0.97; 95% CI: 0.81,1.15; P =0.73).
Bazzano l, Reynolds K et al, 2006 Study Design: Meta-analysis Class: M	N=12 RCTs, representing 16,958 participants, both men and women. Studies were conducted in: • US (two) • Australia and New	Clinical CVD events reported as an end point. Folic acid supplementation with either placebo or usual care.	RR for folic acid supplemental patients vs. control were 0.95 CI: 0.88,1.03 for CVD. RR consistent among participants with pre-existing CVD or renal

Rating:	Zealand (one) • Canada (one) • European countries (eight).	Intervention ranged from 0.5mg per day to 15mg per day, for a duration ranging from six months to five years.	disease.
Bønaa K, Njølstad I et al, 2006 Study Design: Randomized controlled trial Class: A Rating:	Men and women 30 to 85 years of age who had had an acute MI within seven days before randomization from the Norwegian Vitamin (NORVIT) trial, which was a multicenter, prospective, randomized, double-blind, placebo-controlled trial.	Intervention: 1) Combination group: 0.8mg of folic acid, 0.4mg of vitamin B_{12} and 40mg of vitamin B_6 per day 2) 0.8mg of folic acid plus 0.4mg of vitamin B_{12} per day 3) 40mg of vitamin B_6 per day 4) Placebo. Measurements: Primary end point included composite of new non-fatal and fatal MI, non-fatal and fatal stroke and sudden death attributed to CHD. Secondary end points included MI, unstable angina pectoris requiring hospitalization, coronary revascularization with percutaneous coronary intervention or coronary-artery bypass grafting, stroke and death from any cause. Blood samples for plasma total homocysteine serum folate and serum cobalamin.	Treatment with folic acid in combination with vitamin B_{12}, with or without vitamin B_6, did not significantly ↓ risk of the primary end point, as compared with placebo. Both treatment regimens were associated with a NS ↑ in risk, mainly driven by an event rate that was 22% ↑ in the combination-therapy group than in the placebo group (P=0.05). Cumulative HR for the combination-therapy group, as compared with the other three groups, was 1.20 (95% CI: 1.02 to 1.41; P=0.03). Risk of the secondary end points was NS influenced by treatment with folic acid and vitamin B_{12}. Vitamin B_6 therapy associated with a 17% ↑ in the risk of MI (P=0.05) and combination therapy associated with a 30% ↑ in the risk of non-fatal MI (P=0.05).

		Adjustments for: Study center, age, sex, SBP, TC level and smoking status and warfarin use.	
Ebbing M, Bleie O et al, 2008 Study Design: Randomized double-blind controlled trial Class: A Rating:	The Western Norway B-vitamin intervention Trial (WENBIT) was used. Data included men and women ≥18 years undergoing coronary artery angiography for suspected CAD or aortic valve stenosis from two university hospitals in Western Norway.	Intervention treatment consisted of daily oral dose of one of the following: 1) Folic acid, 0.8mg, plus vitamin B_{12} (cyanocobalamin), 0.4mg, and vitamin B_6 (pyridoxine), 40mg 2) Folic acid, 0.8mg, plus vitamin B_{12}, 0.4mg 3) Vitamin B_6, 40mg 4) Placebo.	Mean follow-up: 38 months. Results after one year showed mean serum folate concentration ↑ seven-fold and mean serum cobalamin concentration ↑ by 65% in the groups receiving folic acid plus vitamin B_{12}. Mean plasma total homocysteine level was ↓ by 30%, from 10.8 (SD, 4.5) μmol per L at baseline to 7.6 (SD,2.2) μmol per L in the groups receiving folic acid and vitamin B_{12} ($P<0.001$). In the final results, 422 participants (13.7% of all) experienced an event in the composite primary end point of death, AMI, unstable angina pectoris or thromboembolic stroke. A total of 219 participants (14.2%) in the groups receiving folic acid vs. 203 participants (13.1%) in the groups not receiving folic acid experienced the primary end point (HR= 1.09; 95% CI: 0.90-1.32; P=0.36). 157 participants (12.2%) in the groups receiving folic acid groups vs. 146 (11.8%) of those not receiving folic

			acid experienced the primary end point (HR= 1.04; 95% CI: 0.83,1.30; P= 0.75). No differences in treatment response for the separate end points of death, total AMI (fatal and nonfatal, including procedure-related) or unstable angina pectoris. Incidence of total stroke (fatal and nonfatal, including hemorrhagic) was not significantly ↓ in groups receiving folic acid. Incidence of acute hospitalization due to angina pectoris was ↓ in the folic acid groups (HR= 0.82; 95% CI: 0.67,1.00; P= 0.05). Post hoc overall survival analysis showed no differences between the groups (P= 0.07), but there was an ↑ risk of the composite primary end point in the group receiving folic acid plus vitamin B_{12} (HR=1.34; 95% CI: 1.03,1.75; P= 0.03) compared with placebo.
Ray JG, Kearon C et al, 2007 Study Design: Secondary analysis of data from a randomized trial	Data from the Heart Outcomes Prevention Evaluation 2 (HOPE-2), a large randomized study, were analyzed. N=5,522. Individuals (≥55 years of age with known CVD or DM and at least one	Intervention: Daily supplement of 2.5mg of folic acid, 50mg of vitamin B_6, and 1mg of vitamin B_{12} or matching placebo for five years. Measurement: Prospectively	N=88 episodes of venous thromboembolism, of which about two-thirds were deep venous thrombosis and 47% were unprovoked. N=17 events (19.3%) recorded in the first 18 months after

Class: A Rating:	other risk factor for vascular disease) were recruited from 145 centers in 13 countries: • Canada (N=3,568) • US (N=414) • Brazil (N=265) • Western European countries (N=426) • Slovakia (N=849).	diagnosed and confirmed symptomatic deep venous thrombosis or pulmonary embolism.	randomization and 71 recorded thereafter. N=44 episodes of venous thromboembolism occurred in each group, corresponding to an incidence rate of 0.35 per 100 person-years in each group [HR, 1.01 (95% CI: 0.66 to 1.53); P=0.97]. No benefit observed from the therapy in any subgroup.

Research Design and Implementation Rating Summary
For a summary of the Research Design and Implementation Rating results, click here.

Worksheets

Albert CM, Cook NR, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, Buring JE, Manson JE. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: A randomized trial. *JAMA.* 2008; 299: 2,027-2,036.

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Bønaa KH, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K; NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med.* 2006; 354 (15): 1,578-1,588

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